REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application and for the courteous telephone interview conducted on April 10, 2009 between applicant's undersigned counsel and Examiners Berhanu and Winakur. Applicant's counsel explained how the present invention worked and how it measured AGE content of skin. The Examiners' position was that Kollias '059 taught this. The Examiners suggested adding another feature to the claims to define allowable subject matter. Applicant's counsel took the suggestion under advisement.

The claims have now been amended to add limitations and to more clearly define over the prior art. No new matter has been added. Claims 32, 37, 47, 51-54, 62, 66 and 69-72 have also been amended to change the indication of the subject of the measurements from "patient" into "human individual". For instance from the example set forth at p. 15, l. 4 – p. 16, l. 8 it is clear that the method and apparatus are not only suitable for use on patients, but also on a control group and that the method and apparatus can be useful in screening a population for likelihood of becoming a patient. Although the term "patient" may also be understood as any person subject to medical examination (i.e. not necessarily suffering from an illness or trauma), the term "human individual" is more clear in this respect. Claims 32, 37, 47, 51-54, 62, 66 and 69-72 have also been amended to change the indication "clinically healthy" skin, by the term "non-locally anomalous" since this better distinguishes the measurement from measurements intended to indentify local anomalies and avoids clarity issues regarding the question when a skin is healthy and when it is not.

Listing of rejected claims

Claim 70 has been rejected, but the detailed action mentions no reason for rejecting claim 70. Moreover, corresponding apparatus claim 72 is allowed and similar dependent method claim 37 is only objected, so the rejection of claim 70 may be caused by an error.

Claim rejections – 35 USC § 101

Claims 32 and 62 have been amended to include use of a radiation source, so that the claimed methods are now tied to an apparatus. Moreover the methods involve a transformation of matter

in the sense that skin tissue is irradiated with excitation radiation and thereby transformed from a first state into a second state in which second state the skin tissue emits radiation (or at least more radiation than in the first state) at another wavelength than the wavelength of the excitation radiation.

Claim rejections – 35 USC § 103

Claims 34, 35, 62-68 – Not obvious over Kollias et al. in view of Anderson et al.

Claims 62 and 66 require that:

- the measured autofluorescence is received from a skin tissue surface of at least 0.1 cm^2 and

- the autofluorescence is received only from a portion of the skin surface area that is irradiated with excitation radiation.

Claims 62 and 66 now also require that an advanced glycation/glycosylation end product content for a patient is or can be determined from the measured autofluorescence.

By receiving the fluorescent radiation only from a portion of the skin surface irradiated with excitation radiation, the irradiation of the skin tissue and the measured fluorescence are more uniform over the surface from which fluorescent radiation is received. Variations in irradiation and fluorescence intensity, including scattered irradiation and fluorescence along edges, which are affected by differences in absorption and scattering between different persons, are avoided the more edges of the irradiated surface and the surface from which fluorescent radiation is received do not coincide and are spaced apart. Thus a more precise and better comparable measurement of the AGE content of the skin tissue can be achieved.

In the pending office action it is said that, starting off from Kollias et al., it would have been obvious to arrive at receiving fluorescent radiation from a portion of the irradiated skin surface only, because it can be learned from Anderson et al. (col. 17, l. 55-67) that fiber optic bundles comprising separate radiation and delivery fibers are an alternate equivalent to a fiber optic bundle comprising a single fiber wherein the single fiber both delivers and receives diagnostic radiation to and from the skin.

According to Kollias et al., the radiation is received only from surfaces of the skin that are not irradiated. This is consistent with the purpose of the method according to Kollias et al., which is to measure the blood glucose content and not (primarily) the AGE content in skin tissue. The theoretical principle on which the measurement techniques disclosed by Kollias et al. are based is that the fluorescence is influenced by the presence of glucose at the fluorescent target (col. 3, l. 64 – col. 4, l. 24). Therefore, it would not have been obvious over Kollias et al. to measure fluorescence received from directly irradiated portions of the skin surface, because immediately below the skin surface the blood content is relatively small, and accordingly variations in the blood glucose contents are relatively small. Accordingly, it would also not have been obvious in view over Kollias et al. to select the alternative of using the same optical fiber or fibers for both delivering and receiving radiation.

Moreover, such a substitution of use of the same fiber or fibers for delivering and receiving radiation in Kollias et al. would not result in the feature that the measured fluorescent radiation is received from a portion of the irradiated skin surface only, Instead, using the same fiber for delivering and receiving radiation in Kollias et al. would result in receiving fluorescent radiation from the entire irradiated skin surface.

According to both Kollias et al. and the example of Anderson et al. to which col. 17, l. 55-67 relates (Fig. 6a), the ends of the optical fibers are in contact with the skin. If separate fibers are used for delivering and receiving radiation, as in Kollias et al. and optionally in Anderson et al., the fluorescent radiation is received from portions of the skin surfaces that are not irradiated. If the same fiber or fibers are used for delivering excitation radiation and receiving the fluorescent radiation, the radiation would be delivered and received via the same face or faces of the optical fibers in contact with the skin. Thus, the skin surface from which the fluorescent radiation would be received would be identical to the irradiated skin surface, so the radiation would be received from the entire irradiated skin surface and not only from a portion of the irradiated skin surface as is required by claims 62 and 66.

Thus, the mere combination of a common alternative for the use of the optical fibers as disclosed by Anderson et al. in a method or apparatus according to Kollias et al. would not have resulted in receiving fluorescent radiation from a portion of the irradiated skin surface only. This requires special measures, such a screening off portions of the irradiated skin surface by a measurement window, which are not made obvious by Anderson et al.

With respect to the other (first) example illustrated by Figs. 1 and 2, Anderson et al. it is observed that it would not have been obvious to consider that example, because the use of a camera with a lens and CCD is specifically for identifying local anomalies of the skin. Moreover, also in this example Anderson et al. teaches that the fluorescent radiation is received from the entire irradiated skin surface. According to Anderson et al., col. 11, l. 45-47:

> "*A lens 50 is positioned to couple only fluorescence and reflectance from the area of skin coincident with treatment beam 40 into fiber 48.*".

This confirms the teaching to receive the fluorescent radiation from the entire irradiated surface.

Finally, a more general consideration why it would not have been obvious to measure fluorescent radiation received from a portion of the irradiated skin surface only is, that this entails that, in relation to the amount of light irradiated onto the skin, less fluorescence is received than when the fluorescent radiation would received from the entire irradiated skin surface. Absent the insight that influences of differences in scattering and absorption between subjects have a relatively important influence along the edges of the irradiated surface, it would not have been obvious to receive less fluorescence than technically possible.

Claims 32, 33, 33-40, 43-45, 47, 48, 54-57, 60, 61 – Not obvious over Kollias et al.

Claims 32 and 47 require that the measured autofluorescence is received from an irradiated skin tissue surface of at least 1 cm^2.

Claims 32 and 47 now also require that an advanced glycation/glycosylation end product content for a patient is or can be determined from the measured autofluorescence.

By receiving the fluorescent radiation from an irradiated portion of the skin surface of at least 1 cm^2, the fluorescence is received from surfaces of the skin that are directly irradiated so that differences in scattering and absorption properties have relatively little influence on the measured fluorescence. By measuring over a relatively large surface, at a given total irradiation power, the intensity with which the skin is irradiated is lower than if the same amount of irradiation is concentrated on a smaller surface, so contributions to the fluorescence of skin tissue deeper below the surface, which are affected relatively strongly by absorption and scattering properties are relatively small. Measuring radiation from a large irradiated surface is also advantageous because variations in irradiation and fluorescence intensity, including scattered irradiation and fluorescence along edges, which are affected by differences in

absorption and scattering between different persons, are smaller for a large surface than for a small surface. Thus a more precise and better comparable measurement of the AGE content of the skin tissue can be achieved.

As was argued above, in view of the purpose of the method according to Kollias et al., which is to measure the blood glucose content and not (primarily) the AGE content in skin tissue, it would not have been obvious to measure fluorescence received from directly irradiated portions of the skin surface, because immediately below the skin surface the blood content is relatively small, and accordingly variations in the blood glucose contents are relatively small.

It would have been contrary to the teaching by Kollias et al. col. 5, l. 57-58, that "The portion of the skin irradiated may be less than about 1 square cm, and more preferably is about 0.2 square cm.", and therefore not obvious for the skilled person, to not only provide that the fluorescence is received from the irradiated surface, but also that the area from which the fluorescence is received is larger than 1 square cm. This, in particular in view of the consideration that the more the irradiation is spread over a large surface area, the smaller the relative fluorescence contributions are from layers where (at least according to the theory of Kollias et al.) the blood glucose contents affects the fluorescence. In contrast, for the purpose of measuring the AGE contents of the skin tissue, while avoiding disturbances due to variations in the blood glucose contents, it is advantageous to measure fluorescence from a large, directly irradiated surface, because of the relatively large contribution of fluorescence of the upper layers of the skin that are affected to a relatively small extent by variations in absorption and scattering of the skin tissue.

Thus, since it would not have been obvious over Kollias et al. to provide that the fluorescence is received from a directly irradiated surface area larger than 1 cm^2, the method according to claim 32 and the apparatus according to claim 47 are not obvious over Kollias et al.

Claims 32, 35, 36, 47, 49, 50, 56-58 and 66 - Not obvious over Anderson et al.

Claims 32, 47, and 66 now also require that an advanced glycation/glycosylation end product content for a patient is or can be determined from the measured autofluorescence.

Anderson et al. discloses methods and systems for scanning a patient's skin, designating areas of affected skin, and selectively delivering high doses of phototherapeutic ultraviolet radiation to the designated areas (col. 2, l. 39-42).

For developing a method according to claim 32 or an apparatus according to claims 47 and 66, which determine an AGE content for a patent, it would not have been obvious to take a scanning apparatus as disclosed by Anderson et al. as starting point.

Furthermore, the disclosed spot size of the tracer beam at the patient's skin (which determines the size of the surface area from which autofluorescence can be simultaneously received) is: less than about 1 cm, and is typically about 1 to 4 mm. The skilled person would readily recognize that increasing the spot size would result in deteriorating the resolution of the scanning result and, accordingly, deteriorating the accuracy at which the skin areas affected by psoriasis and to be treated with the high doses of phototherapeutic ultraviolet radiation can be designated. Treating healthy skin with high doses of phototherapeutic ultraviolet radiation is clearly undesirable. Therefore, increasing the spot size in the methods and systems according to Anderson et al. would be counterproductive to the very purpose thereof and would therefore not be obvious. Therefore, it would not have been obvious to modify Anderson et al. in the sense that the fluorescence is simultaneously received from an area larger than 1 cm^2. Therefore, the method and apparatus according to claims 32 and 47 are not obvious over Anderson et al.

As observed earlier, Anderson et al. teaches that the measured light is received from a skin area coincident with the illuminated skin area. In the technical context of Anderson et al. receiving the fluorescence from a portion of the irradiated surface only, would only resulting a smaller image obtained via the CCD camera and accordingly a longer time required to scan the body parts of interest for psoriasis. Accordingly, it would not have been obvious over Anderson et al. to receive the fluorescence only from a portion of the irradiated skin surface. Therefore, it would not have been obvious over Anderson et al. to provide an apparatus as claimed in claim 66.

For all the foregoing reasons, it is believed that all of the claims now present in this application are in condition for allowance, which is respectfully requested.

If any further fees are required by this communication, please charge such fees to our Deposit Account No. 16-0820, Order No. VOB-34537US1.

Respectfully submitted,
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